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Population pharmacokinetics of total and unbound plasma cisplatin in adult patients

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Aims
To investigate the pharmacokinetics of unbound (ultrafilterable) and total plasma platinum using a population approach and to identify patient characteristics that may influence the disposition of the drug.

Methods
Pharmacokinetic and demographic data were collected from adult patients treated with 30-min daily infusions of cisplatin for various malignancies. Unbound and total platinum concentration-time data were analysed using a nonlinear mixed effects model.

Results
Data from 43 patients were available for analysis. A linear two-compartment model best described total and unbound platinum plasma concentration-time data. The mean population estimates for total and unbound drug were, respectively, 0.68 and 35.5 l h^{-1} for clearance and 21.1 and 23.4 l for central distribution volume (V_1). Unbound clearance (CL) was dependent on body surface area (BSA) and creatinine clearance, and V_1 was dependent on BSA. The elimination rate constant for plasma-bound platinum (modelled as metabolite formation) was 0.014 h^{-1}. The pharmacokinetic parameter, f_m/V_m, a measure of the clearance of unbound platinum due to irreversible plasma binding, was related to serum protein concentration and to the inverse of dose per m^2. The covariate modelling of CL, V_1 and f_m/V_m improved the intersubject variabilities associated with these parameters. The final pharmacokinetic models were validated using 200 bootstrap samples from the original datasets.

Conclusions
The results support the conventional dose adjustment of cisplatin based on BSA. They also support the need for a dose reduction in case of renal insufficiency.

Introduction

Cisplatin is widely used to treat numerous solid tumours. Because of a strong relationship between dose and response, an important issue in cisplatin chemotherapy is the dose intensity [1]. Neurotoxicity, ototoxicity and myelosuppression, and severe nephrotoxicity may occur after normal dosing regimens. Thus, there is a requisite to determine *a priori* cisplatin doses and schedules that will provide therapeutic benefit and cause minimum toxicity. The population approach is a useful tool in estimating mean pharmacokinetic parameters in patients, and in identifying individual characteristics that can influence pharmacokinetics and decrease intersubject variability.

Since cisplatin undergoes irreversible protein binding in plasma, the potentially active form is thought to be that which is unbound in the circulation. However, the relationship between unbound and bound (total minus unbound) plasma cisplatin concentrations has not been modelled.

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The objectives of this study were: (i) to estimate the population pharmacokinetic parameters of unbound and total plasma platinum, (ii) to investigate the influence of demographic and physiological variables on the pharmacokinetic parameters of interest, and (ii) to establish a pharmacokinetic model that simultaneously describes the time-course of unbound and total plasma platinum concentrations, allowing the characterization of plasma protein-bound platinum pharmacokinetics.

Because there were only 43 patients in this study, the stability and predictive performance of each population pharmacokinetic model were assessed using a bootstrap procedure.

Methods

Patients

Patients were receiving cisplatin as part of two Phase I studies in the Laboratory of Pharmacology at the Centre René Huguenin. Cisplatin was combined with either irofulven, 0.4 mg kg^{-1} as a 30-min infusion, or with 5-fluorouracil, 1 g m^{-2} day^{-1} as a continuous 120-h infusion. Patients were diagnosed with metastatic cancer and were receiving second- or third-line chemotherapy. The institution (Comite d'Ethique de Saint-Germain-en-Laye, France) approved the protocols and informed consent was obtained from each patient.

Drug administration, blood sampling and sample preparation

Cisplatin in normal saline solution was administered as a 30-min intravenous infusion, for 5 consecutive days or twice a month. The total dose per infusion varied between 15 and 80 mg. Blood samples were taken after the end of the infusion and at 0.25, 0.45, 0.75, 1, 1.5, 2, 4, 6, 8, 12 and 24 h after start of infusion.

After immediate centrifugation at $1500 \times g$ for 10 min, the plasma was separated and an aliquot was ultrafiltered through an Amicon MPS I micropartition system (Millipore France, Saint Quentin, France) with YMT membranes at 4 °C for 30 min at $2000 \times g$. All samples were immediately frozen at −20 °C until analysis.

Analysis of platinum

Cisplatin concentrations were measured by flameless atomic absorption spectrophotometry (AAS) as described previously [2]. Briefly, platinum was determined using a Zeemann AAS apparatus (Varian, Les Ulis, France) under the following conditions: drying phase 130 °C, pyrolysis 1300 °C and atomization 2850 °C. Standards were prepared in plasma and distilled water for total plasma and ultrafiltrate concentrations, respectively, by using a Platinum Atomic Absorption standard solution (0.980 mg ml^{-1}) (Sigma P6401, Sigma, Saint Quentin, France). The lower limit of determination was 20 μg l^{-1}.

Population pharmacokinetic modelling

Data analysis was performed using a nonlinear mixed-effect model program, MP2 [3]. The pharmacokinetics of unbound (the parent compound), total (unbound +irreversibly protein-bound platinum) and unbound-total platinum were studied sequentially.

Basic pharmacokinetic and statistical models The pharmacokinetics of unbound and total cisplatin was each ascribed a two-compartment model with linear elimination. The parameters of the basic pharmacokinetic model were CL, the systemic clearance; V_1 and V_2, the central and peripheral compartment volumes; and Q, the intercompartmental clearance. The proportional error model with constant coefficient of variation, and the additive random effects model were used to describe intersubject (ISV) and residual variabilities. Extensive graphical analysis of predicted *vs.* observed (PRED *vs.* OBS) concentrations was performed to test the value of each model. In addition, comparison between the mean of the individual Bayesian parameter estimates and the population mean estimates served to discriminate between the error models.

Modelling of covariate effects The influence of each patient covariate on pharmacokinetic parameters was systematically tested, using CL as an example, according to the following equation:

$$\mathrm{CL} = TV(\mathrm{CL}) \times [\mathrm{BW}/\mathrm{median}(\mathrm{BW})]^{\theta.\mathrm{BW}}$$

where TV(CL) is the typical value of clearance for a patient with the median covariate value and θBW is the estimated determining factor for body weight. Such covariates included age, body weight (BW), body surface area (BSA), serum creatinine concentration (SCr), serum protein concentrations (PROT), dose m^{-2}, creatinine clearance (CLCr) and concomitant drug administration (irofulven or 5-fluorouracil).

The effect of categorical covariates was modelled; with respect to gender, for example

$$\mathrm{CL} = TV(\mathrm{CL}) \text{ for males}$$

$$\mathrm{CL} = TV(\mathrm{CL}) \times \theta_{\mathrm{gender}} \text{ for females}$$

where GENDER equals 1 for males and 2 for females, and θ_{gender} describes the relative change in CL of females with respect to males.

Full and reduced models (one parameter less) were compared by the χ^2 test of the difference between their respective objective function values (OFV). The effect of a covariate was considered to have improved the fit if there was a significant decrease in the OFV of at least 7 ($P < 0.01$) compared with the basic pharmacokinetic model (with no covariate), along with a decrease in the ISV of the associated pharmacokinetic parameter. An intermediate multivariate model was then obtained including all significant covariates. In order to keep only those covariates with the largest contribution in the final multivariate model, a change of 11 ($P < 0.001$, one degree of freedom) of the OFV was required for the retention of a single parameter during backward stepwise multiple regression analysis.

Step 1. Total plasma platinum concentration-time courses were first analysed according to a two-compartment open model.

Step 2. Unbound plasma platinum concentration-time courses were then analysed according to a two-compartment open model.

Step 3. The pharmacokinetic parameters of the unbound final population model, including covariate effects, were then used to incorporate the input function into the metabolite, protein-bound platinum, compartment as depicted in Figure 1. The pharmacokinetic parameters for unbound platinum were fixed and the protein-bound platinum parameters were estimated, f_m/V_m (f_m, metabolite-to-parent clearance fraction, V_m, metabolite volume) and CL_{m0}/V_m (CL_{m0}, metabolite clearance). V_m is not identifiable in this model.

Bootstrap validation

The accuracy and robustness of the final population model were assessed using a bootstrap method [4]. Briefly, this includes the following steps: (i) from the original dataset of n individuals, B bootstrap sets (usually 200) of n individuals are drawn with replacement (resampling)] (ii) for each of the B bootstrap sets, the population pharmacokinetic parameters are estimated; (iii) with the B estimates of each population pharmacokinetic parameter, the corresponding mean, median and standard deviation are estimated; (iv) to validate the model, the mean parameters estimated from the bootstrap must be in a reasonably close agreement with estimates obtained from the original population set.

Limited-sampling model

Given the population pharmacokinetic parameters, the theoretical optimal sampling times were determined by means of the program OSP-Fit, based on random search and stochastic gradient algorithms [5]. Two sets of four optimal sampling times were generated for unbound and total plasma cisplatin, each set corresponding to 15 patients.

Results

A total of 483 plasma samples were available from 43 patients, producing 396 unbound and 477 total plasma concentrations. Eighteen and 25 patients received concomitant irofulven or 5-fluorouracil chemotherapy, respectively. The latest sampling times with quantifiable total cisplatin concentrations were 24–25 h after infusion. Most samples were taken between 0.4 and 6.5 h. The infusion time, typically 0.5 h, varied from 0.25 to 1 h over 146 infusions. One to five consecutive daily infusions were available for pharmacokinetic evaluation. Patient characteristics are summarized in Table 1.

Figure 2 depicts the total plasma platinum concentration-time profiles. After several analyses with various residual error models, the additive error model was applied. ISVs were ascribed to proportional error models.

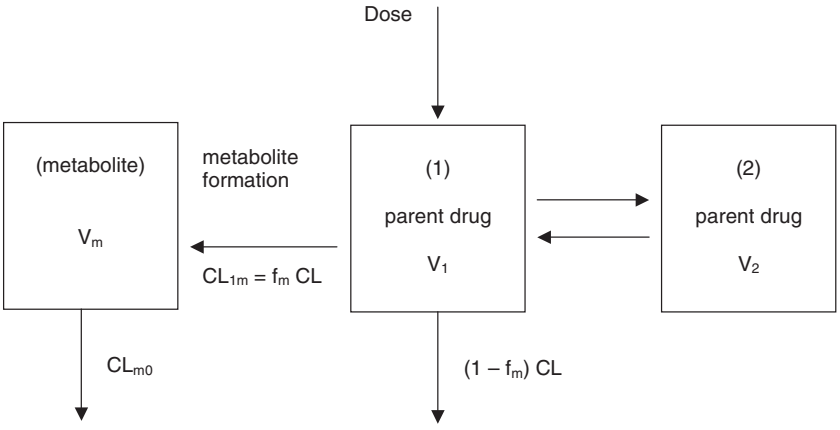

Figure 1
Scheme for the pharmacokinetic compartment model for the simultaneous prediction of total and unbound (ultrafilterable) plasma platinum concentrations after cisplatin infusion. Unbound platinum can exchange between compartments 1 and 2, and can undergo irreversible plasma binding from compartment 1 to produce plasma protein-bound platinum in compartment 'm'. *V* and CL denote the volume and clearance terms, respectively. *Q* is the intercompartmental clearance, f_m is the metabolite clearance fraction of plasma-unbound platinum. The subscripts 1, 2 and m refer to the unbound platinum and protein-bound platinum plasma species, respectively

Table 1
Characteristics of the 43 patients (male/female, 25/18) studied

Characteristics	Mean	Median	Range
Age (years)	55	58	21–76
Body weight (kg)	63	64	40–102
Height (cm)	167	168	150–181
Body surface area (m^2)	1.69	1.62	1.38–2.10
Serum proteins ($g\ l^{-1}$)	68	70	47–80
Serum creatinine ($\mu mol\ l^{-1}$)	77	76	43–120
Dose (mg)	35.5	34.4	20–80
Creatinine clearance* ($ml\ min^{-1}$)	84	81	44–155
Dose m^{-2} per infusion ($mg\ m^{-2}$)	25	25	15–40
Unbound cisplatin concentration ($ng\ ml^{-1}$)	414	342	20–1960
Total cisplatin concentration ($ng\ ml^{-1}$)	800	650	124–2790

**According to the Cockcroft and Gault formula.*

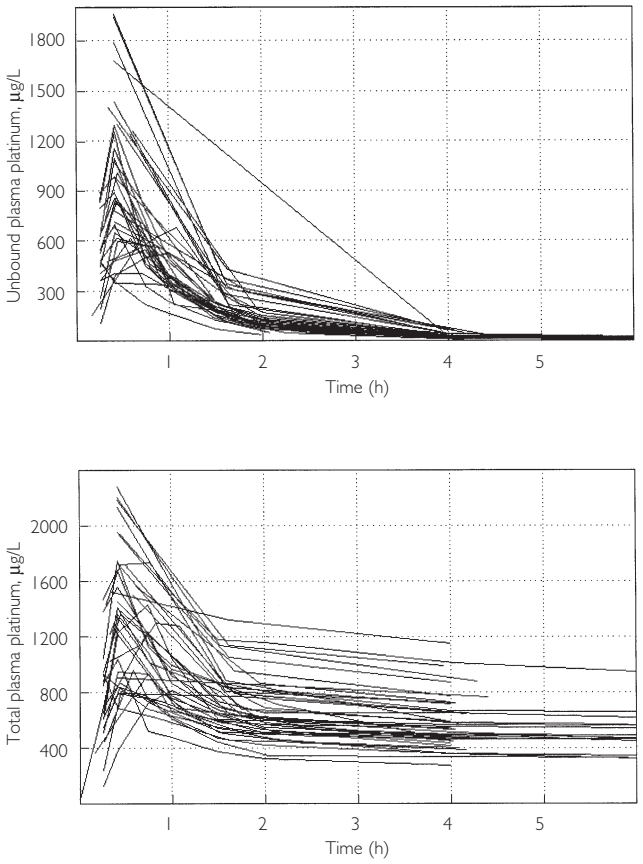

Figure 2
Observed total and unbound platinum plasma concentration-time courses during the first 6 h after the start of infusion

Table 2
Summary of covariate effects on cisplatin (platinum) pharmacokinetic parameters (only significant effects are reported)

Pharmacokinetic parameter	Covariate(s)	OFV decrease	ISV (%)
Total platinum			
V_1	None	0	42
V_1	Gender	−11	36
V_1	BSA, BW	−24, −20	27, 30
UF platinum			
V_1	None	0	32
V_1	Gender†	−16	23
V_1	BSA, BW	−22, −14	22, 22
CL	None	0	23
CL	Gender†	−12	19
CL	BSA, BW	−17, −12	17, 18
CL	CLCr	−15	17
UF + bound platinum			
f_m/V_m*	None	0	27
f_m/V_m	Serum proteins	−11	24
f_m/V_m	Dose m^{-2}‡	−17	23.5

*ISV, Intersubject variability; BSA, body surface area; BW, body weight. *fm was previously corrected for CL covariate effects. †The estimate was lower in females than in males. ‡Inverse relationship between parameter and covariate.*

Table 3
Population pharmacokinetic parameters for total plasma cisplatin in 43 patients and bootstrap validation (477 total platinum concentration-time measurements)

	Final model		
	Original dataset	Bootstrap*	
Parameter	Mean	Mean	SE
Structural model			
V_1 (l)	21.1	21.0	1.0
V_1, θ_{BSA}	+2.30	+2.14	0.41
CL (l h^{-1})	0.68	0.67	0.08
Q (l h^{-1})	22.2	22.2	1.6
V_2 (l)	42.6	43.3	4.0
Statistical model			
Res. Error (μg l^{-1})	162	161	28
ISV(V_1) (% CV)	27.4	25.7	8.5
ISV(CL) (% CV)	39.1	38.8	18.8
ISV(Q) (% CV)	32.5	31.9	15.7
ISV(V_2) (% CV)	35.0	34.7	15.3
Derived parameters			
$T_{1/2}$, distribution (h)	0.45	NA	NA
$T_{1/2}$, elimination (h)	66.8	NA	NA

**Mean of 200 bootstrap analyses. SE, Standard error of estimate; V_1, V_2, central and peripheral distribution volumes; CL and Q, elimation clearance and intercompartmental clearance; BSA, body surface area; NA, not applicable; Res. Error, residual variability; ISV, interindividual variability; % CV, coefficient of variation in %.*

Table 2 summarizes the covariate modelling step. The final population model included BSA as a significant covariate for V_1, decreasing the ISV from 42 to 27%. Table 3 summarizes the population parameters and the bootstrap validation. Observed *vs.* model-predicted total plasma platinum concentrations are depicted in Figure 3.

Figure 2 depicts the unbound plasma platinum concentration-time profiles. Statistical modelling was identical to that applied to total platinum concentrations. The data did not allow reliable estimations of intersubject variabilities for Q and V_2 and fixing these parameters to zero did not increase the OFV and did not alter the pharmacokinetic estimates. Table 2 summarizes the covariate modelling process. BSA and BW were positively related to both V_1 and CL. V_1 and CL were smaller in female than in male patients. Finally, CL was positively related to CLCr. BSA and BW were strongly correlated (r = 0.953). Thus, given the improvements in OFV and ISV, BW was dropped and BSA was retained in the model. The correlation between BSA and CLCr

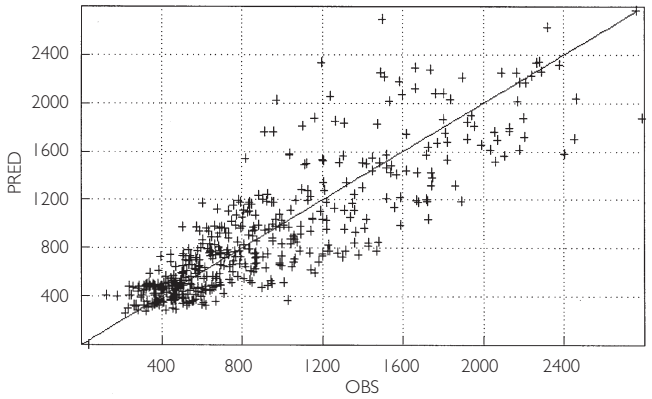

Figure 3
Predicted (PRED) from the final pharmacokinetic model and observed (OBS) total platinum plasma concentrations

was much weaker (0.355), and keeping both covariates in the CL modelling improved the fit. Finally, the gender effect on V_1 and CL was no longer significant and the final covariate models were

$$V_1 = 23.4 \times (BSA/1.70)^{2.3}$$

$$CL = 35.5 \times (BSA/1.70)^{0.83} \times (CLCr/81)^{0.36}$$

The ISVs for CL and V_1 decreased from 23 and 32% (covariate-free model) to 15 and 23%, respectively. Table 4 summarizes the population parameters. The observed *vs.* model-predicted unbound plasma platinum concentrations are depicted in Figure 4.

The plasma protein-bound platinum pharmacokinetics was modelled as a metabolite compartment connected to the central compartment (Figure 1). The unbound cisplatin pharmacokinetic parameters, including the covariate effects, were fixed and plasma protein-bound platinum parameters were estimated from the simultaneous analysis of unbound and total plasma concentrations. The error models for unbound and plasma protein-bound platinum were identical to the previous ones, including specific estimates for unbound and plasma-bound platinum residual variabilities. The covariate effects for plasma-bound platinum pharmacokinetic parameters are summarized in Table 2. The following equation describes the final covariate model for plasma protein-bound platinum formation, CL_{1m}:

$$CL_{1m} = f_m/V_m \times CL = TV(CL_m) \times (\text{dose } m^{-2}/25)^{-0.48} \times (PROT/70)^{1.33}$$

or in terms of f_m/V_m:

$$f_m/V_m = TV(f_m/V_m) \times (\text{dose } m^{-2}/25)^{-0.48} \times (PROT/70)^{1.33} \times (BSA/1.7)^{-0.83} \times (CLCr/81)^{-0.36}$$

Table 4
Population pharmacokinetic parameters of unbound plasma cisplatin in 43 patients and bootstrap validation (396 unbound platinum concentration-time measurements)

Parameter	Final model Original dataset Mean	Bootstrap* Mean	Bootstrap* SE
Structural model			
V_1 (l)	23.4	23.0	1.0
V_1, θ_{BSA}	+1.60	+1.53	0.34
CL (l h^{-1})	35.5	35.6	1.4
CL, θ_{BSA}	+0.83	+0.83	0.31
CL, θ_{CLCr}	+0.36	+0.36	0.18
Q (l h^{-1})	8.64	8.89	1.44
V_2 (l)	12.0	12.6	5.33
Statistical model			
Res. Error (μg l^{-1})	116	115	16
ISV(V_1) (% CV)	23.4	22.3	7.5
ISV(CL) (% CV)	14.9	14.5	7.6
Derived parameters			
$T_{1/2}$, distribution (h)	0.34	NA	NA
$T_{1/2}$, elimination (h)	1.32	NA	NA

**Mean of 200 bootstrap analyses. SE, Standard error of estimate; V_1, V_2, central and peripheral distribution volumes; CL and Q, elimination clearance and intercompartmental clearance; BSA, body surface area; NA, not applicable; Res. Error, residual variability; ISV, interindividual variability; % CV, coefficient of variation in %.*

Table 5
Population pharmacokinetic parameters of plasma protein-bound cisplatin in 43 patients and bootstrap validation (platinum, 396 plasma unbound +477 total plasma concentration-time measurements)

Parameter	Final model Original dataset Mean	Bootstrap* Mean	Bootstrap* SE
Structural model			
f_m/V_m (l^{-1})	0.017	0.017	0.001
f_m/V_m, $\theta_{DOSEm^{-2}}$	–0.48	–0.50	0.16
f_m/V_m, θ_{PROT}	+1.33	+1.27	0.42
f_m/V_m, θ_{BSA}	–0.83 (fixed)	NA	NA
f_m/V_m, θ_{CLCr}	–0.36 (fixed)	NA	NA
CL_{m0}/V_m (h^{-1})	0.014	0.014	0.002
Statistical model			
Res. Error (μg l^{-1})	103	104	35
ISV(f_m/V_m) (% CV)	21.4	20.5	9.8
ISV(CL_m/V_m) (% CV)	31.8	31.2	10.6
Derived parameters			
$T_{1/2}$, elimination (h)	50	NA	NA

**Mean of 200 bootstrap analyses. SE, Standard error of estimate; f_m, fraction metabolized, fraction of unbound platinum clearance that undergoes irreversible plasma protein binding; CL_m, elimation clearance of metabolite, i.e. of plasma-bound platinum; BSA, body surface area; PROT, serum proteins; CLCr, creatinine clearance; NA, not applicable; Res. Error, residual variability; ISV, interindividual variability; % CV, coefficient of variation in %.*

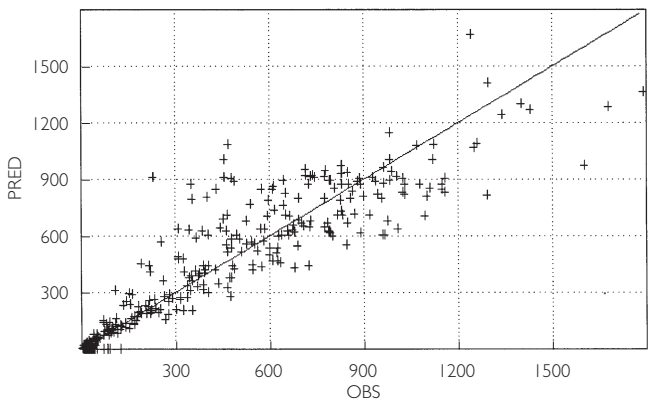

Figure 4
Predicted (PRED) from the final pharmacokinetic model and observed (OBS) unbound platinum plasma concentrations

where only the exponents for the dose m^{-2} and PROT covariate effects were estimated. The ISV estimate for f_m/V_m decreased from 27 to 21% (the respective contributions of dose m^{-2} and PROT covariates to this ISV reduction were, respectively, −2.5 and −3.5). Table 5 summarizes the population parameters. Figure 5 depicts curve-fittings obtained by Bayesian estimation using this population model in two representative patients.

The mean parameter estimates obtained from the bootstrap process, 200 runs, were statistically identical to the estimates previously obtained with the original dataset (Tables 3, 4 and 5). Moreover, the bootstrap procedure provided reliable estimates of accuracy for the population parameters.

For unbound cisplatin pharmacokinetics, it was reasonable to limit the last sampling time to 6 h. Then, the optimized sampling times (OST) were 0.5, 1, 3.3 and 4.5 h after the start of infusion. For total cisplatin pharmacokinetics, the OST were 0.5, 1, 4 and 24 h. If both

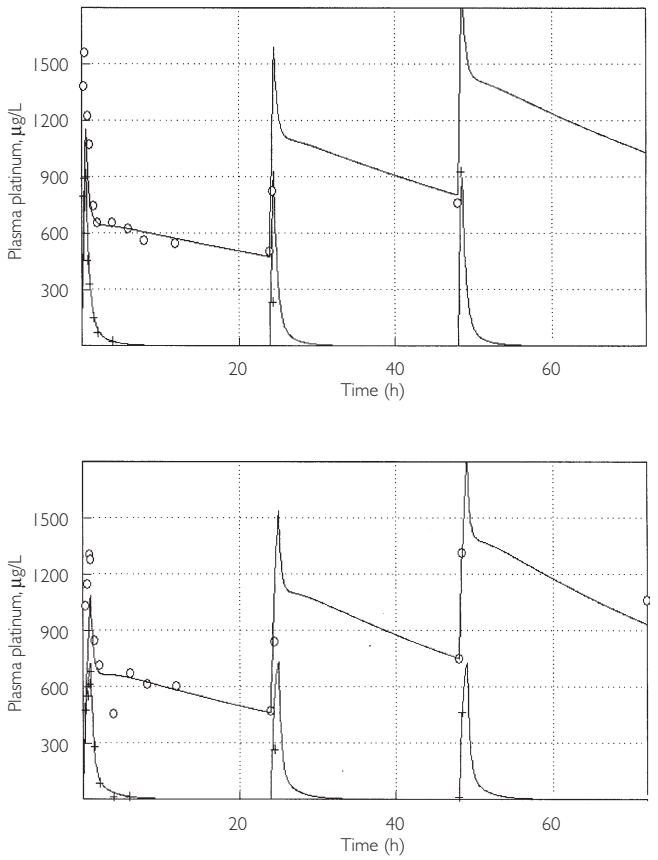

Figure 5
Concentration-time profiles of unbound platinum (+) and total platinum (○) from two patients. Curves are drawn according the model depicted in Figure 1

unbound and total cisplatin pharmacokinetics are to be investigated, sampling times of 4 h and 24 h are recommended.

Discussion

The pharmacokinetics of unbound and total plasma cisplatin was satisfactorily described by two-compartmental open models as previously reported [6–8]. For total plasma platinum, clearance was in the order of previously reported estimates for short-term infusions (< 3 h), i.e. 1.4 l h^{-1} [9], 1 l h^{-1} per 64 kg [7] and 0.54 l h^{-1} [8]. Furthermore, the clearance of unbound plasma platinum was in the range of previous estimates, i.e. 13 [7], 32 [6], 35.2 [10], 42.5 [11] and 43 l h^{-1} [9]. Clearances were multiplied by 1.7 m^2 or 64 kg when values were reported per m^2 or per kg, respectively.

The covariate modelling resulted in improved goodness-of-fit for both total and unbound platinum pharmacokinetics. The relationship between BSA or BW and the central distribution volume of either total or unbound platinum is self-explanatory. The covariate structure for clearance has a major importance, because it may aid in the design of dosage regimens. Since unbound cisplatin is partly eliminated by the kidney, a significant relationship with CLCr, a marker of renal function, was not unexpected. Relationships between BSA or BW, body size parameters, and CL are frequently observed. The relationship with BSA and cisplatin CL has been reported previously [11–13].

The present study showed high consistency in the final unbound platinum/plasma-bound platinum population model derived from sequential analyses of unbound platinum and plasma-bound platinum, confirming the robustness of the process. To our knowledge, there have been no reports of integrated modelling of unbound platinum/plasma-bound platinum pharmacokinetics. Theoretically, the pharmacokinetics of a metabolite produced from a drug whose pharmacokinetics is described by a two-compartment model have a three-exponential decay profile. Our data did not allow the identification of three exponential components for total plasma platinum. Thus, only an integrated model of unbound platinum/plasma-bound platinum pharmacokinetics could provide a reliable estimate of the terminal half-life of plasma-bound platinum, since the information for the rapid exponential decays is provided by unbound platinum data. Indeed, using the population approach, data on the parent drug may add information to the observations on the metabolite [14].

The integrated pharmacokinetic model indicated that f_m/V_m, which relates to the fraction of the dose inactivated by plasma protein binding, was significantly related to serum protein concentration and inversely related to the administered dose per m^2. Plasma protein binding is known to be related to protein concentration. The negative effect of the dose per m^2 covariate indicated that, at highest doses, the relative contribution of plasma protein-binding to clearance should be decreased. The half-life, 50 h, for the terminal plasma decay of plasma-bound cisplatin was close to that estimated for total plasma platinum. Indeed, the later plasma samples contain mainly the plasma-bound species.

In conclusion, this study described population models for unbound and total plasma cisplatin pharmacokinetics derived from 43 patients. The results support the conventional adjustment of dose based on body area. Moreover, patients with renal impairment should be given a lower dosage than patients with normal renal function. The proposal of a limited sampling strategy, along with a knowledge of the patient characteristics that influence pharmacokinetics, should improve the

design of future pharmacokinetic studies for optimizing therapy with cisplatin.

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